REMARKS

I. Status of the Claims

This submission is in response to the non-final Office Action electronically mailed on December 11, 2009. Claims 1, 2 and 4-36 are pending, claims 18 and 19 having been withdrawn by the Examiner. Accordingly, claims 1, 2, 4-17 and 20-36 are pending and at issue.

Claims 1, 21 and 26 have been amended to recite an antimicrobial agent selected from benzalkonium chloride, disodium EDTA, or a combination thereof. Previously, an antimicrobial agent was optionally included in the claimed controlled release compositions, and a weight ratio of morphine:chitosan was recited. Support for this amendment can be found, for example, in the Examples that begin on page 10 of the application as-filed. Claims 10-12 have been amended to recite amounts in "mg/ml" as opposed to "% weight/volume." Support for this amendment can be found, for example, at page 7, lines 22-30 of the application as-filed. Claims 13 and 14 have also been amended for purposes of clarity, and claim 14 has also been amended to depend from claim 1 instead of claim 12. No new matter has been added by way of these amendments.

As noted in the Interview Summary dated January 22, 2010, the outstanding Office Action is a non-final Office Action.

Applicants request reconsideration of this application in view of the amendments and remarks below. Applicants thank the Examiner for her careful consideration of this application.

II. Objections to the Specification

The Examiner notes that the specification does not provide proper antecedent basis for claims 10-12. According to the Examiner, claims 10-12 recite the amount of

antioxidants in terms of % weight/volume, however pages 7-8 discuss the presence of antioxidants in terms of mg/ml. Claims 10-12 have been amended to recite the specified amounts in terms of mg/ml, rendering this objection moot. Applicants appreciate the Examiner's attention to this detail.

III. Rejections Under 35 U.S.C. § 103

A. Rejections Over Illum

Claims 1-2, 4-9, 12, 16-17 and 20-36 stand rejected as obvious over U.S. Patent No.6,387,917 issued to Illum et al. (hereafter "Illum"). As correctly noted by the Examiner, however, Illum does not disclose the use benzalkonium chloride or disodium EDTA. Independent claims 1, 21, 26 have been amended to recite an antimicrobial agent selected from benzalkonium chloride, disodium EDTA, or a combination thereof. Accordingly, Applicants request that this rejection be withdrawn.

B. Rejections Over Illum in view of Grebow

Claims 13-15 stand rejected as obvious over Illum in view of U.S. Patent No. 5,026,825 issued to Grebow et al. (hereafter "Grebow"). According to the Office Action:

> While Illum discloses the use of antimicrobial agents, Illum does not disclose the use of benzalkonium chloride, disodium EDTA, sodium benzoate, and combinations thereof.
>
> Grebow discloses an intranasal formulation comprising antimicrobial agents including benzalkonium chloride and disodium EDTA (Examples). They are present in the amount of 0.001-2.0% (w/v) (column 11, lines 55-63).
>
> It would have been obvious to one of ordinary skill in the art at the time the invention was made to have incorporated the specific antimicrobial agents of Grebow into the formulation of Illum since Grebow discloses [that] they are suitable for use in nasal inhalant formulation.

(Office Action at 5-6). Applicants respectfully disagree that the Office Action has established a *prima facie* case of obviousness and request reconsideration in view of the following remarks.

A *prima facie* case of obviousness must establish that (1) there is some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings; (2) there is a reasonable expectation of success; and (3) the prior art reference (or references when combined) teach or suggest all the claim limitations. *See* M.P.E.P. §§ 706.02(j) and 2143. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, rather than Applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 U.S.P.Q2d 1438 (Fed. Cir. 1991).

At least because there would have been no reasonable expectation of successfully substituting the antimicrobial agents in Grebow's calcitonin formulation with the morphine formulations disclosed in Illum to provide a stable formulation, a *prima facie* case of obviousness has not been established. Grebow's formulations are limited to calcitonin, and analogs thereof. A person of ordinary skill in the art would have no expectation of successfully combining antimicrobial agents used in a calcitonin formulation (a polypeptide hormone), with morphine (a small molecule opiate analgesic) to provide a stable formulation. In this regard, the Federal Circuit has noted that the development of pharmaceuticals is highly unpredictable. *See, e.g., Ortho-McNeil v. Mylan Labs*, 520 F.3d 1358 (Fed. Cir. 2008).

Furthermore, the compositions of Grebow require the use of Δ-aminolevulinic acid, which "inhibits the degradation of calcitonin" (Grebow at col. 1, lines 11-12). Δ-aminolevulinic acid is present in each and every formulation disclosed in Grebow. A person of ordinary skill in the art would understand that Δ-aminolevulinic acid is a central tenant of the

Grebow disclosure, as it is required to prevent the calcitonin from degrading, and is thus necessary to provide for a stable formulation. (*See* Grebow at col. 1., lines 47-47-50, which notes degradation problems encountered by intranasal formulations that do not contain Δ-aminolevulinic acid.)

Unlike Grebow, however, Illum does not disclose use of Δ-aminolevulinic acid. One of ordinary skill in the art, without benefit of the present disclosure, would have no expectation that the particular antimicrobial agents disclosed in the calcitonin/Δ-aminolevulinic acid formulations of Grebow could be incorporated into the morphine formulations of Illum, which do *not* contain Δ-aminolevulinic acid to provide a stable formulation.

At least because a person of ordinary skill in the art would have no expectation of successfully incorporating the particular antimicrobial agents of Grebow into the morphine formulations of Illum, Applicants respectfully submit that a *prima facie* case of obviousness has not been established. Accordingly, Applicants request that the obviousness rejection be withdrawn and the application passed to issuance.

Conclusion

In view of the above amendments and remarks, it is respectfully requested that the application be passed to allowance. If there are any other issues remaining which the Examiner believes could be resolved either through a Supplemental Response or an Examiner's Amendment, the Examiner is respectfully requested to contact the undersigned at the telephone

number indicated below. Applicants believe no fee is due at this time. However, if any fees are required, the Commissioner is authorized to charge such fee to Deposit Account No. 02-4377.

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Respectfully submitted,

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